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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,328	12/07/1999	KUBER T. SAMPATH	CIBT-P01-514	9813

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/445,328	SAMPATH ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5,6,8,9,11,12,14-38 and 53-57* is/are pending in the application.

4a) Of the above claim(s) *21,22,25 and 28-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5,6,8,9,11,12,14-20,23,24,26,27,35-38 and 53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *2,5,6,8,9,11,12,14-38 and 53-57* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 11/12/2004 has been entered. Claims 2, 5, 6, 8, 9, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 53, 54, 55, 56, 57 are pending. Applicant's election with traverse of Group X, the species OP-1, the species the mature form of OP-1, the species pre-renal causes of acute renal failure, the species decreased cardiac output, and the species intravenous administration in the paper mailed 08/06/2002 is acknowledged. Claims 21, 22, 25, 28-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper mailed 08/06/2002.

Applicant's election of GFR in the reply filed on 03/01/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2, 5, 6, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 53, 54, 55, 56, 57 are being examined only to the extent they read upon the elected invention and/or species.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 103

Claims 2, 5, 6, 8, 9, 11, 12, 14, 23, 24, 26, 27, 35, 36, 37, 38, 53, 56, 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (U) in view of Kuberasampath (AG, cited by Applicants) and Lefer (V).

Claims 2, 15-20, 53, 54, 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (U) in view of Kuberasampath (AG, cited by Applicants) and Lefer (V) as applied to claims 2, 53 above, and further in view of Anderson (U, the paper mailed 12/16/2002) and Brady (W).

Applicants argue that the Office assumes that if an agent is known to reduce inflammation, then one skilled in the art would reasonably expect that agent to be effective in treating acute renal failure. Based on this assumption, Applicants argue, the Office concludes that since OP-1 is allegedly effective in treating inflammation, then one skilled in the art would reasonably expect OP-1 to be effective in treating acute renal failure. Applicants argue that at the time the present application was filed, anti-inflammatory agents, and in particular anti-inflammatory agents which decrease leukocyte adhesiveness and/or ICAM expression, were known to decrease renal function, or even to cause outright renal failure. Accordingly, the skilled artisan would have expected that OP-1 would have aggravated, not improved, renal function in a mammal afflicted with acute renal failure. Applicants rely upon:

(1) TGF-β1 has 35% amino acid sequence identity with the 7-Cys domain of OP-1 (Exhibit A) and their binding to cell surface receptors which activate Smad proteins.

TGF-β was known to have anti-inflammatory activity (Exhibits B and C). However, TGF-β1 was known to cause and/or aggravate renal disease (Exhibits D, E, and F). Therefore, the skilled artisan would not have expected TGF-β1 would be effective in treating ARF and would have expected OP-1, like TGF-β1, to decrease renal function in mammal afflicted with ARF.

(2) CsA is an anti-inflammatory agent that suppresses ICAM-1 expression (Exhibits G and H). CsA reduces renal function (Exhibit I). Therefore, the skilled artisan would have expected that OP-1, like CsA, would reduce renal function. Exhibits G, H, and I teach away from using OP-1 to treat renal failure.

(3) NSAIDs are anti-inflammatory agents that inhibit neutrophil adhesion (Exhibit J). NSAIDs reduce renal function and contribute to renal failure (Exhibits K, L, and M). Therefore, the skilled artisan would have expected that OP-1, like NSAIDs, would reduce renal function. Exhibits K, L, and M teach away from using OP-1 to treat renal failure.

Applicant's arguments have been fully considered but they are not persuasive.

Applicants' argument that the structural similarity between OP-1 and TGF-β1 and their functional similarities of signaling through Smad proteins would lead the skilled artisan to expect OP-1, like TGF-β1, to decrease renal function is conclusory and unsupported. In fact, the fictional differences between OP-1 and TGF-β are well documented:

> OP-1 promotes cell condensations and tubulogenesis in E11.5 metanephric mesenchyme, while TGF-β1 had no effect on metanephric differentiation under identical conditions. The growth of E11.5 cultures, as determined by DNA and protein content, was comparable to both OP-1 treated and untreated control, while TGF-β1 reduced the growth in E11.5 kidney cultures. Vukicevic et al. Proc Natl Acad Sci U S A. 1996 Aug 20;93(17):9021-6, see page 9023, paragraph bridging left and right columns, and page 9024, paragraph bridging left and right columns.

> Direct comparison of TGF-beta 1 and hOP-1 in these bone cell cultures indicated that, although both hOP-1 and TGF-beta 1 promoted cell proliferation and collagen synthesis, only hOP-1 was effective in specifically stimulating markers of the osteoblast phenotype. Sampath et al. J Biol Chem. 1992 Oct 5;267(28):20352-62, see the Abstract.
>
> OP-1 induces both chondroblastic and osteoblastic differentiation of osteoprogenitor cells derived from newborn rat calvaria. TGF-β1 fails to induce any hypertrophic chondrocytes, and in combination with OP-1, TGF-β1 blocks OP-1-dependent chondroinduction. Asahina et al. J Cell Biol. 1993 Nov;123(4):921-33, see the Abstract.

There is no evidence of record that OP-1 possesses any of the renal side-effects of TGF-β1, CsA, or NSAIDs. Therefore, evidence that TGF-β1, CsA, or NSAIDs reduce renal function cannot rebut the prima facie case of obviousness.

There is no evidence of record that inhibition of inflammation or neutrophil adherence cause any of the renal side-effects of TGF-β1, CsA, or NSAIDs. Therefore, the argument that the skilled artisan would expect that OP-1 could not be used to treat ARF, because some agents that inhibit inflammation or neutrophil adherence have renal side-effects, cannot rebut the prima facie case of obviousness.

The fact that Kelly's suggest that agents designed to block leukocyte-endothelial interactions mediated via ICAM-1 may be therapeutically effective in the prevention and treatment of acute renal failure (page 1062, left column, full paragraph 2) and suggest a critical role for leukocytes and adhesion molecules, in particular ICAM-1, in the pathophysiology of ischemic acute renal failure that may have important therapeutic implications for the treatment of acute renal failure in humans (page 1062, left column, full paragraph 3); the fact that Kuberasampath teaches that OP-1 is useful for administering to an animal to inhibit the tissue destructive effects associated with the body's inflammatory response, including repairing

damaged tissue, and/or inhibiting additional damage thereto (page 9, full paragraphs 1-2), that OP-1 reduces or prevents the immune cell-mediated cellular destruction at extravascular sites of recent tissue destruction, but also prevents or reduces the continued entry of immune effector cells into extravascular sites of ongoing inflammatory cascades (page 38, line 3, through page 40, line 9), that the morphogens further enhance the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue (page 40, full paragraph 2), and that hOP-1 exhibits significant anti-adherent actions on PMNs (Lefer, page 592, left column, second sentence) provides a reasonable expectation of success.

Applicants argue that the references fail to teach or suggest improving a standard marker of renal function. Applicant's arguments have been fully considered but they are not persuasive. The fact that damage to cells resulting from the effects of an inflammatory response by immune cell mediated tissue destruction has been implicated as the cause of reduced tissue function or loss of tissue function in the kidney, and the fact that OP-1 reduces or prevents the immune cell-mediated cellular destruction at extravascular sites of recent tissue destruction, prevents or reduces the continued entry of immune effector cells into extravascular sites of ongoing inflammatory cascades, disrupts the functional interaction of immune effector cells with endothelium where the adhesion molecules are induced by means other than in response to tissue injury, and further enhances the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue, provides a reasonable expectation that administration of OP-1 to a mammal afflicted with acute renal failure would effect an improvement in a standard marker of renal function. This also suggest that one of ordinary skill in the art would administer OP-1 to a mammal afflicted with acute renal failure with the intent of effecting an improvement

in a standard marker of renal function. Furthermore, Anderson (U, the paper mailed 12/16/2002) teaches that ARF is characterized by a reduction in the glomerular filtration rate (page 1294, left column, last paragraph), suggesting that one of ordinary skill in the art would administer OP-1 to a mammal afflicted with acute renal failure with a reasonable expectation and the intent of effecting an improvement in GFR. The fact that Applicants have recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.

Applicants argue that the references cited by Applicants teach away from using OP-1 to improve a marker of renal function because anti-inflammatory agents where known to decrease renal function. Applicants argue that the references cited by Applicants' would lead one of ordinary skill in the art to use agents with no anti-inflammatory properties and would lead one of ordinary skill in the art away from the path of treating subjects with dialysis. Applicant's arguments have been fully considered but they are not persuasive. Applicants rely upon:

(1) TGF-β1 has 35% amino acid sequence identity with the 7-Cys domain of OP-1 (Exhibit A) and their binding to cell surface receptors which activate Smad proteins. TGF-β was known to have anti-inflammatory activity (Exhibits B and C). However, TGF-β1 was known to cause and/or aggravate renal disease (Exhibits D, E, and F). Therefore, the skilled artisan would not have expected TGF-β1 would be effective in treating ARF and would have expected OP-1, like TGF-β1, to decrease renal function in mammal afflicted with ARF.

(2) CsA is an anti-inflammatory agent that suppresses ICAM-1 expression (Exhibits G and H). CsA reduces renal function (Exhibit I). Therefore, the skilled artisan would have

expected that OP-1, like CsA, would reduce renal function. Exhibits G, H, and I teach away from using OP-1 to treat renal failure.

(3) NSAIDs are anti-inflammatory agents that inhibit neutrophil adhesion (Exhibit J). NSAIDs reduce renal function and contribute to renal failure (Exhibits K, L, and M). Therefore, the skilled artisan would have expected that OP-1, like NSAIDs, would reduce renal function. Exhibits K, L, and M teach away from using OP-1 to treat renal failure.

Applicant's arguments have been fully considered but they are not persuasive.

Applicants' argument that the structural similarity between OP-1 and TGF-β1 and their functional similarities of signaling through Smad proteins would lead the skilled artisan to expect OP-1, like TGF-β1, to decrease renal function is conclusory and unsupported. In fact, the fictional differences between OP-1 and TGF-β are well documented:

> OP-1 promotes cell condensations and tubulogenesis in E11.5 metanephric mesenchyme, while TGF-β1 had no effect on metanephric differentiation under identical conditions. The growth of E11.5 cultures, as determined by DNA and protein content, was comparable to both OP-1 treated and untreated control, while TGF-β1 reduced the growth in E11.5 kidney cultures. Vukicevic et al. Proc Natl Acad Sci U S A. 1996 Aug 20;93(17):9021-6, see page 9023, paragraph bridging left and right columns, and page 9024, paragraph bridging left and right columns.
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> Direct comparison of TGF-beta 1 and hOP-1 in these bone cell cultures indicated that, although both hOP-1 and TGF-beta 1 promoted cell proliferation and collagen synthesis, only hOP-1 was effective in specifically stimulating markers of the osteoblast phenotype. Sampath et al. J Biol Chem. 1992 Oct 5;267(28):20352-62, see the Abstract.
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> OP-1 induces both chondroblastic and osteoblastic differentiation of osteoprogenitor cells derived from newborn rat calvaria. TGF-β1 fails to induce any hypertrophic chondrocytes, and in combination with OP-1, TGF-β1 blocks OP-1-dependent chondroinduction. Asahina et al. J Cell Biol. 1993 Nov;123(4):921-33, see the Abstract.

There is no evidence of record that OP-1 possesses any of the renal side-effects of TGF-β1, CsA, or NSAIDs. Therefore, evidence that TGF-β1, CsA, or NSAIDs reduce renal function does not teach away from using OP-1 to improve renal function.

There is no evidence of record that inhibition of inflammation or neutrophil adherence cause any of the renal side-effects of TGF-β1, CsA, or NSAIDs. Therefore, evidence that some agents that inhibit inflammation or neutrophil adherence have renal side-effects does not teach away from using OP-1 to improve renal function.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
MAY 11, 2005